

Exhibit A

United States Patent [19][11] **Patent Number:** **5,969,156****Briggs et al.**[45] **Date of Patent:** ***Oct. 19, 1999**

[54] **CRYSTALLINE [R- (R*,R*)]-2-(4-DFLUOROPHENYL)- β , δ -DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID HEMI CALCIUM SALT (ATORVASTATIN)**

[51] **Int. Cl.⁶** **C07D 207/335; A01N 43/36**
[52] **U.S. Cl.** **548/537; 514/423; 514/429**
[58] **Field of Search** **548/537; 514/423, 514/429**

[56] **References Cited****U.S. PATENT DOCUMENTS**

5,316,765 5/1994 Folkers et al. 424/94.1

FOREIGN PATENT DOCUMENTS0409281 7/1990 European Pat. Off. .
9416693 8/1995 WIPO .**OTHER PUBLICATIONS**

Bocan, Thomas et al., Antiatherosclerotic activity of inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, *Atherosclerosis*, 111, 127-142, Dec. 1994.

Tetrahedron Letters, vol. 33, No. 17, 1992, pp. 2283-2284, Baumann, et al.

Pharmaceutical Research, vol. 10, No. 10, 1993, pp. 1461-1465, Kearney, et al.

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[57] **ABSTRACT**

Crystalline forms of atorvastatin and hydrates thereof are useful hypolipidemic and hypocholesterolemic agents.

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[73] **Assignee:** **Warner-Lambert Company**, Morris Plains, N.J.

[*] **Notice:** This patent is subject to a terminal disclaimer.

[21] **Appl. No.:** **08/945,812**

[22] **PCT Filed:** **Jul. 8, 1996**

[86] **PCT No.:** **PCT/US96/11368**

§ 371 Date: **Oct. 2, 1997**

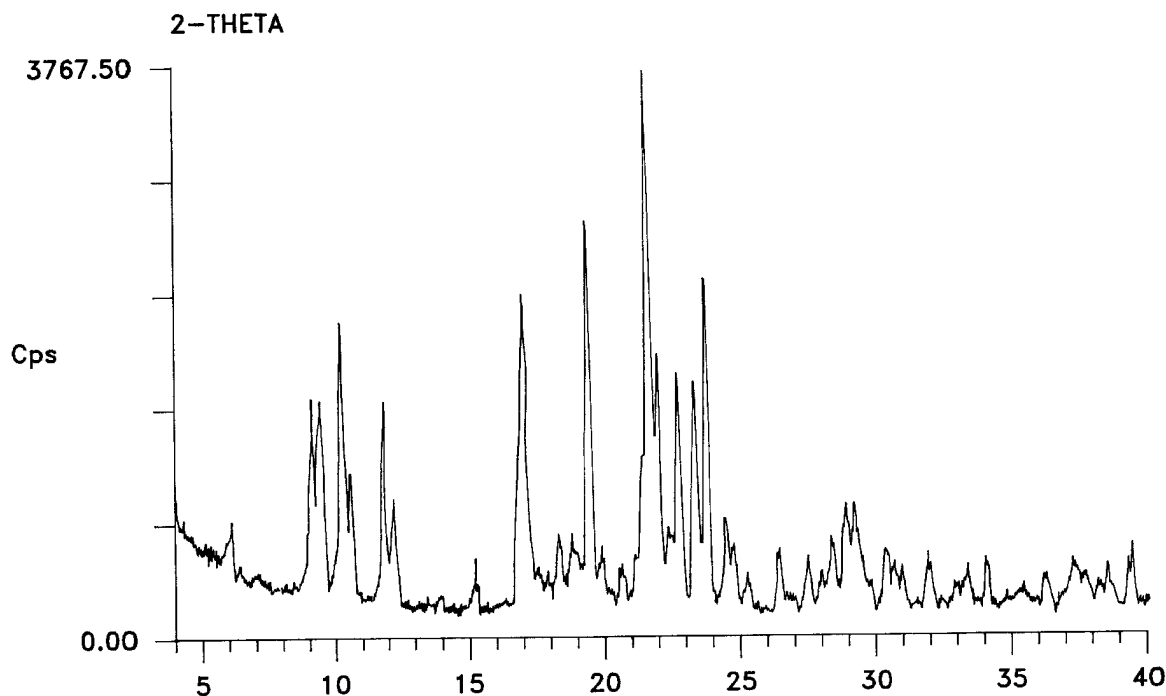
§ 102(e) Date: **Oct. 2, 1997**

[87] **PCT Pub. No.:** **WO97/03959**

PCT Pub. Date: Feb. 6, 1997

Related U.S. Application Data

[60] **Provisional application No. 60/001,452, Jul. 17, 1995.**

44 Claims, 6 Drawing Sheets

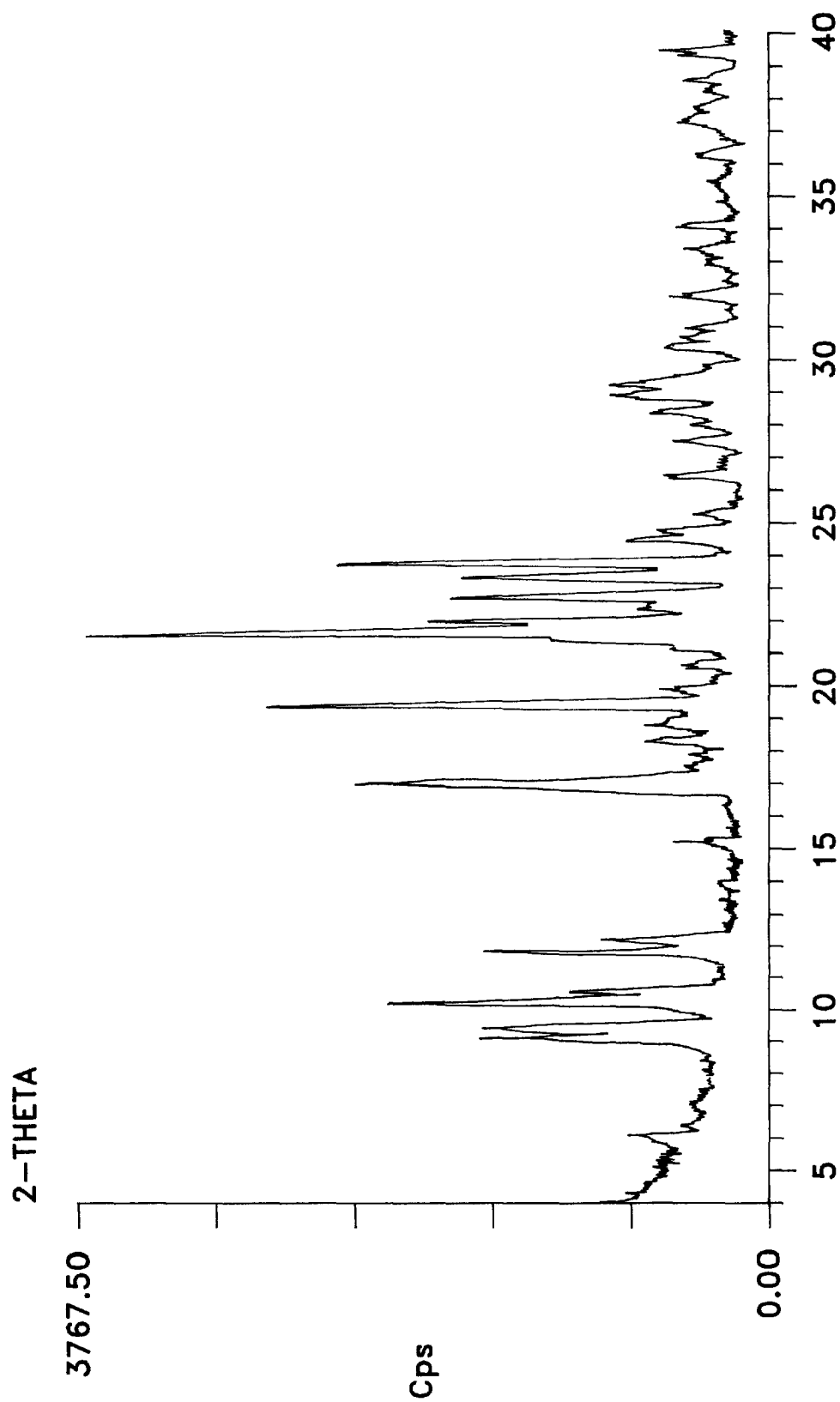
U.S. Patent

Oct. 19, 1999

Sheet 1 of 6

5,969,156

FIG-1



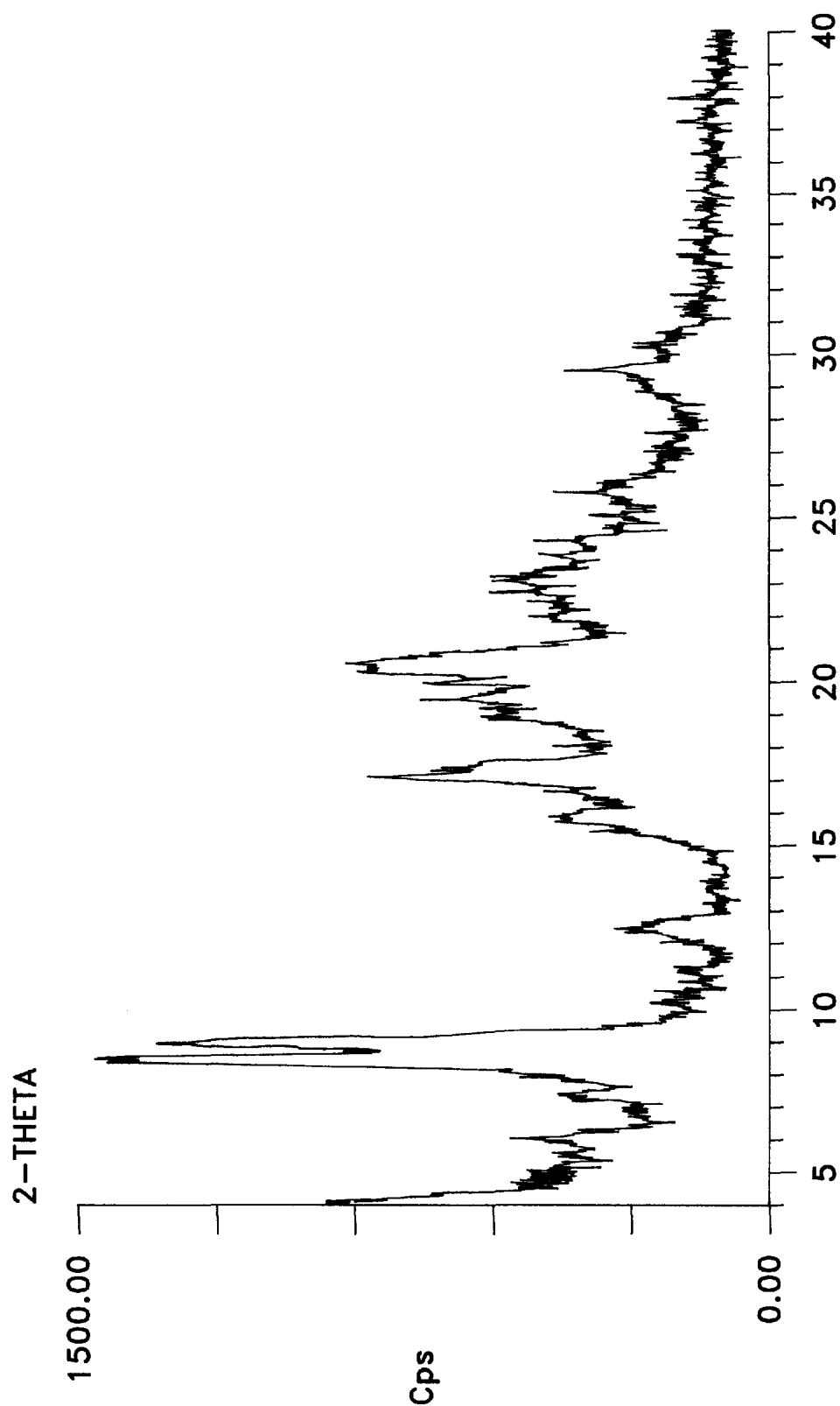
U.S. Patent

Oct. 19, 1999

Sheet 2 of 6

5,969,156

FIG-2



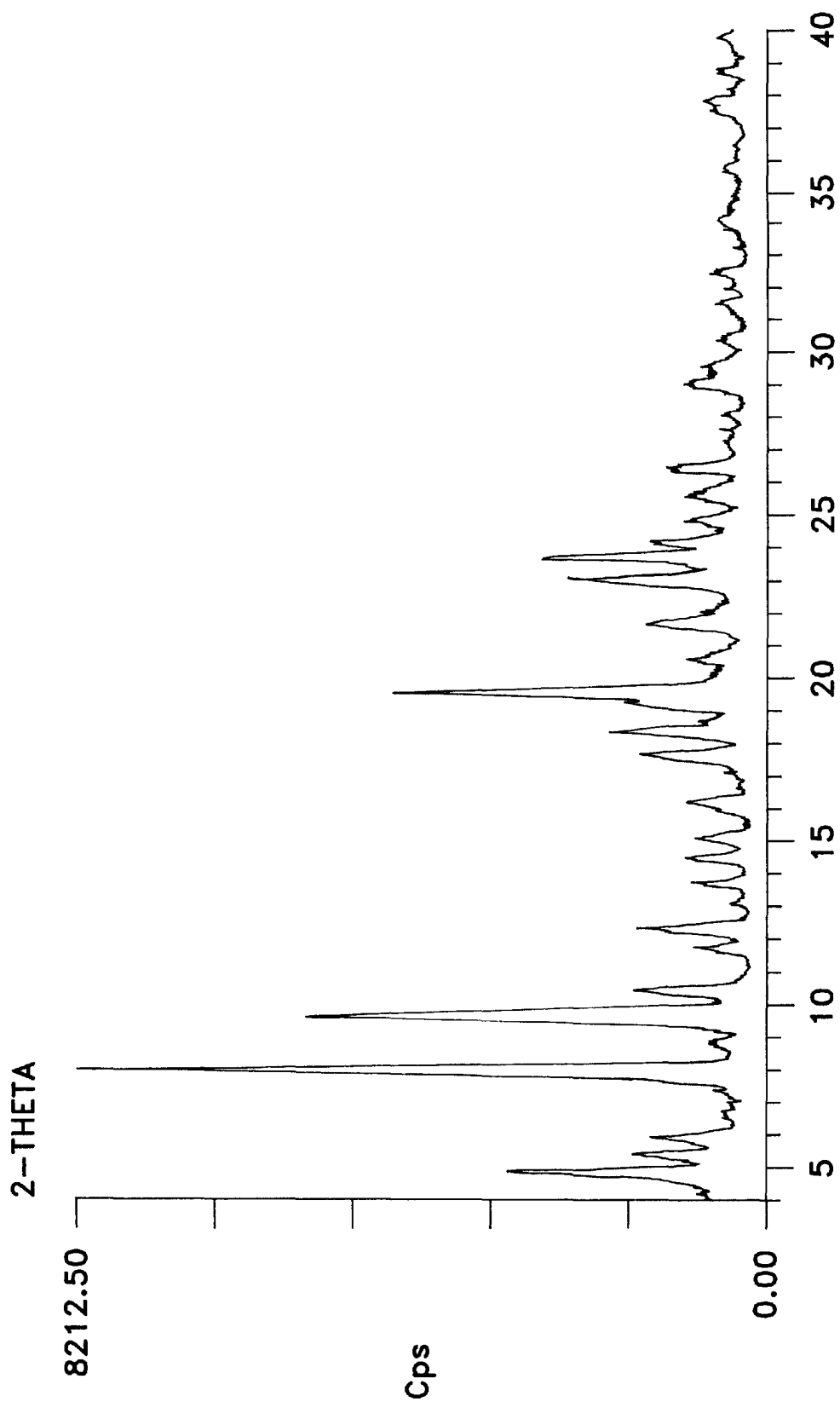
U.S. Patent

Oct. 19, 1999

Sheet 3 of 6

5,969,156

FIG-3



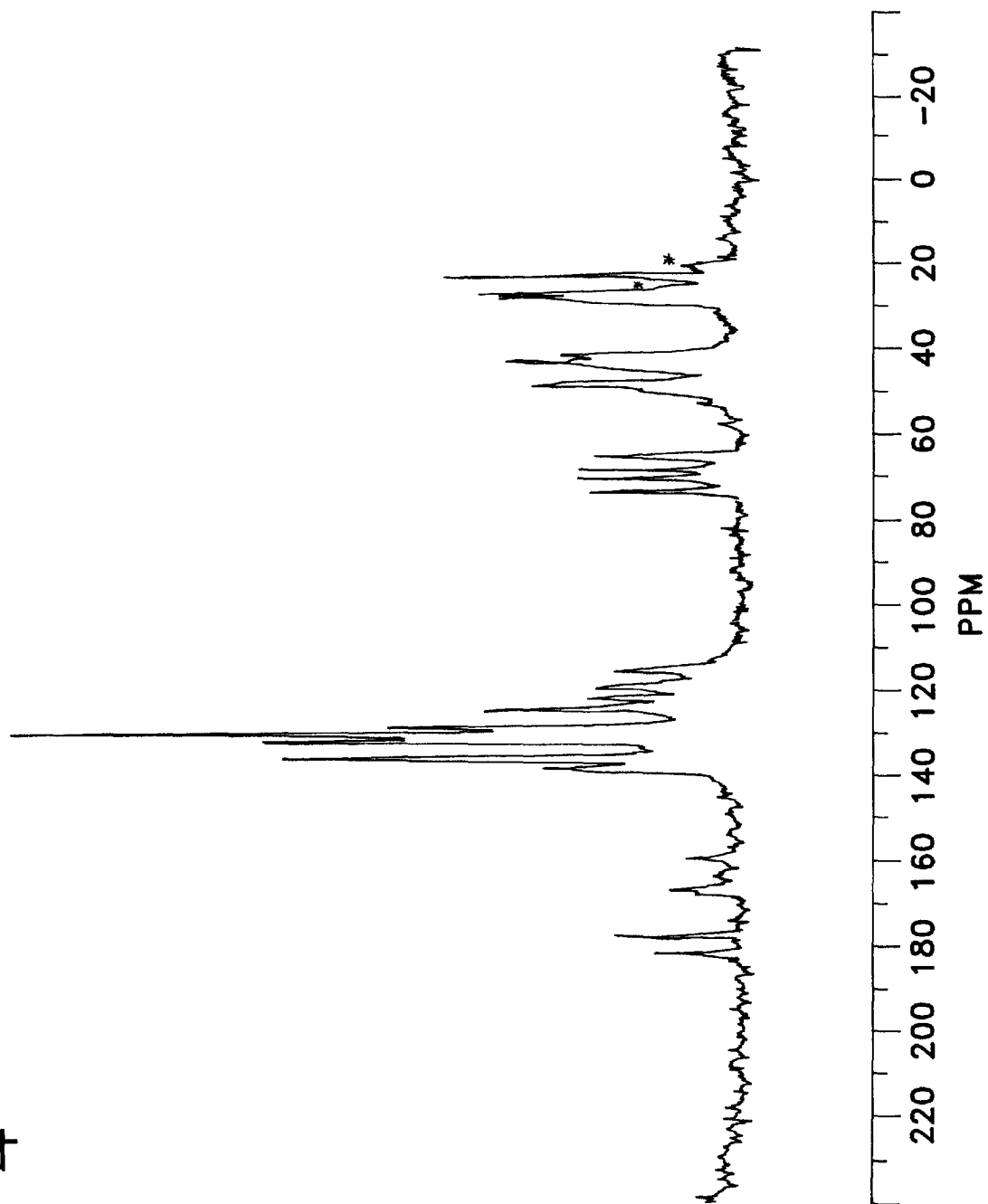
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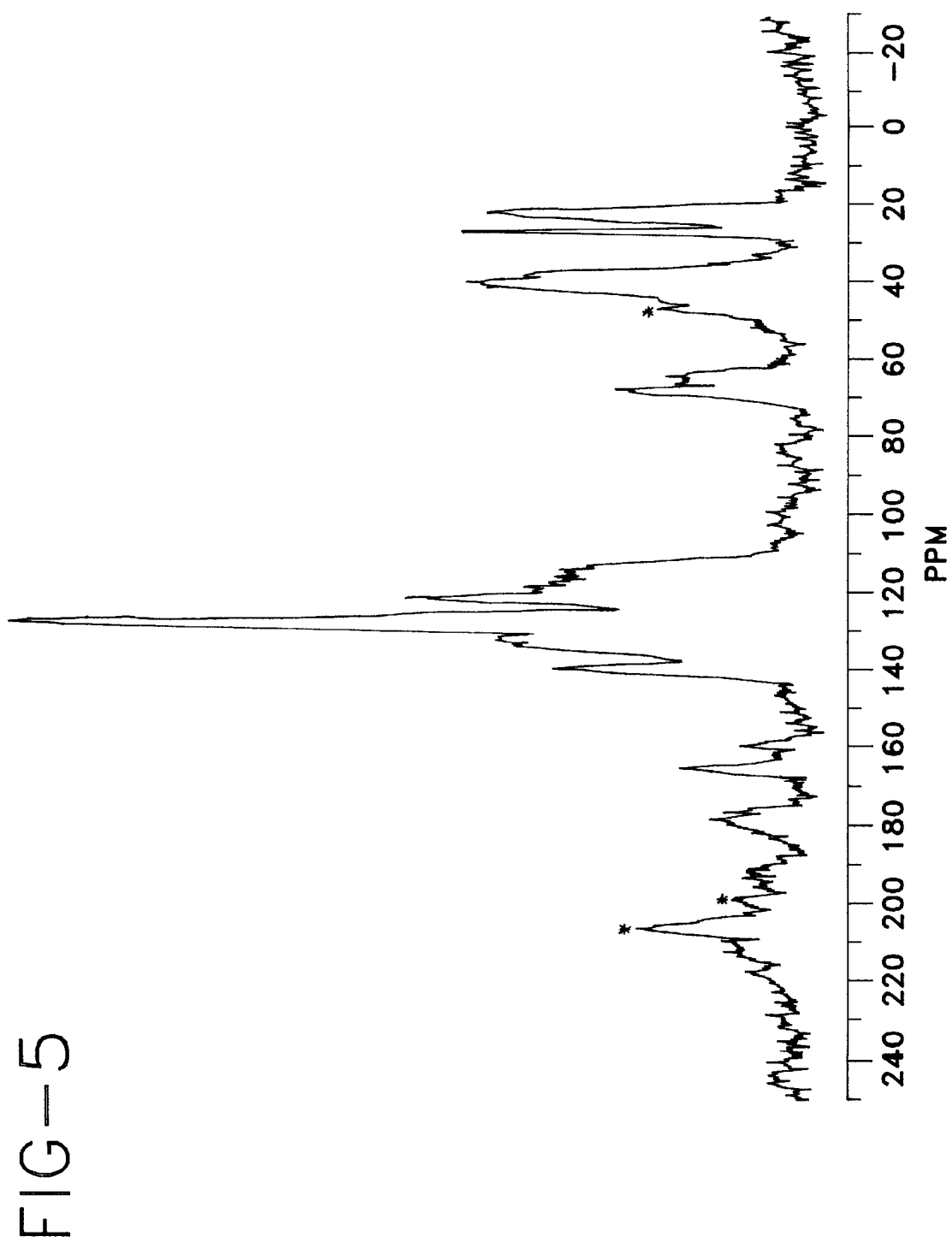
Oct. 19, 1999

Sheet 4 of 6

5,969,156

FIG-4





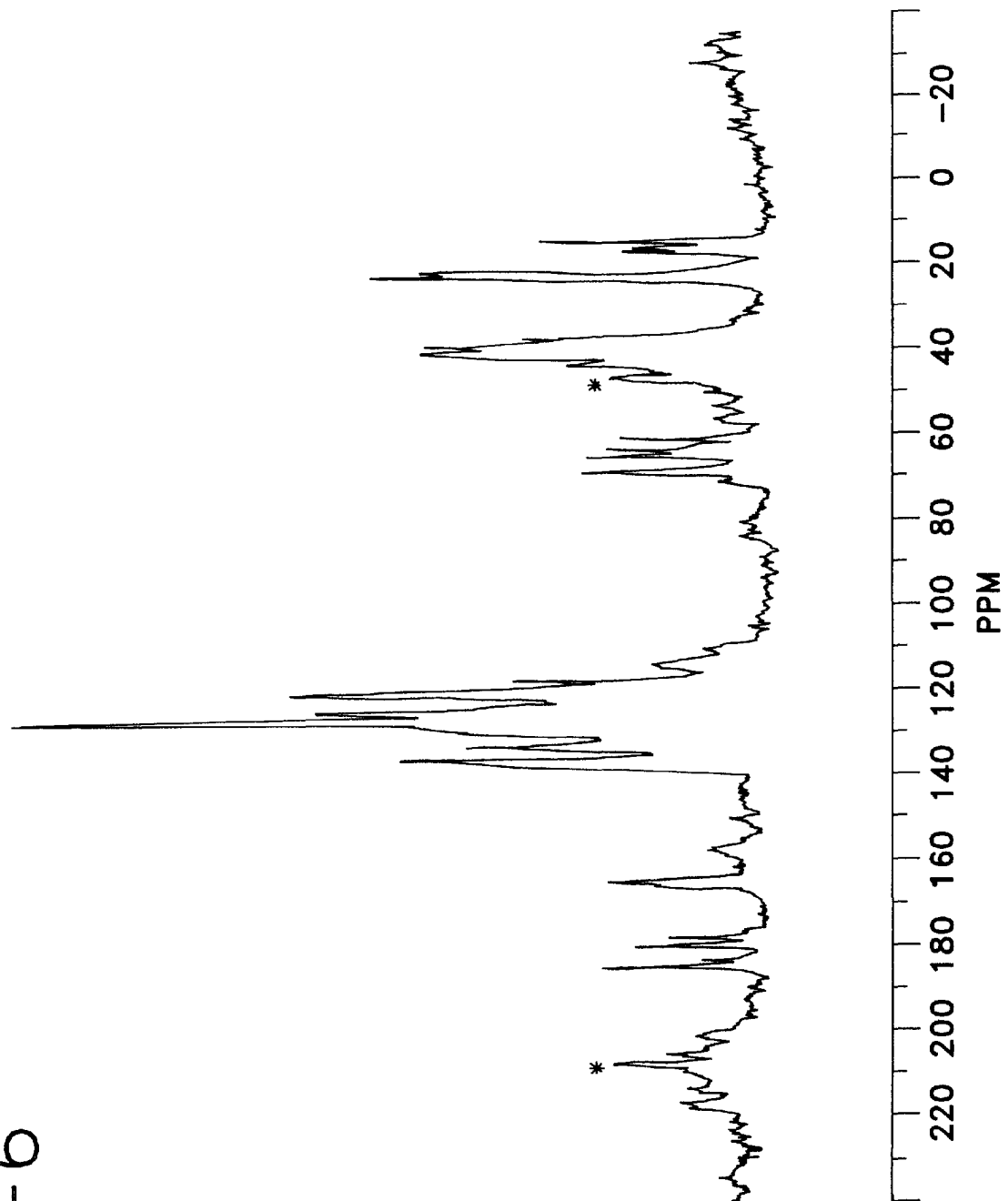
U.S. Patent

Oct. 19, 1999

Sheet 6 of 6

5,969,156

FIG-6



5,969,156

1

**CRYSTALLINE [R- (R*,R*)]-2-(4-
 DFLUOROPHENYL)- β , δ -DIHYDROXY-5-(1-
 METHYLETHYL)-3-PHENYL-4-
 [(PHENYLAMINO)CARBONYL]-1H-
 PYRROLE-1-HEPTANOIC ACID HEMI
 CALCIUM SALT (ATORVASTATIN)**

This application is a 371 of PCT/US96/11368 filed Jul. 8, 1996 which is a continuation of Provisional Application No. Ser. 60/001,452, filed Jul. 17, 1995.

BACKGROUND OF THE INVENTION

The present invention relates to novel crystalline forms of atorvastatin which is known by the chemical name [R-(R*, R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt useful as pharmaceutical agents, to methods for their production and isolation, to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment. The novel crystalline compounds of the present invention are useful as inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) and are thus useful hypolipidemic and hypocholesterolemic agents.

U.S. Pat. No. 4,681,893, which is herein incorporated by reference, discloses certain trans-6-[2-(3- or 4-carboxamido-substituted-pyrrol-1-yl)alkyl]-4-hydroxy-pyran-2-ones including trans (\pm)-5-(4-fluorophenyl)-2-(1-methylethyl)-N, 4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

U.S. Pat. No. 5,273,995, which is herein incorporated by reference, discloses the enantiomer having the R form of the ring-opened acid of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, i.e., [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid.

U.S. Pat. Nos. 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,280,126; 5,397,792; and 5,342,952, which are herein incorporated by reference, disclose various processes and key intermediates for preparing atorvastatin.

Atorvastatin is prepared as its calcium salt, i.e., [R-(R*, R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). The calcium salt is desirable since it enables atorvastatin to be conveniently formulated in, for example, tablets, capsules, lozenges, powders, and the like for oral administration. Additionally, there is a need to produce atorvastatin in a pure and crystalline form to enable formulations to meet exacting pharmaceutical requirements and specifications.

Furthermore, the process by which atorvastatin is produced needs to be one which is amenable to large-scale production. Additionally, it is desirable that the product should be in a form that is readily filterable and easily dried. Finally, it is economically desirable that the product be stable for extended periods of time without the need for specialized storage conditions.

The processes in the above United States Patents disclose amorphous atorvastatin which has unsuitable filtration and drying characteristics for large-scale production and must be protected from heat, light, oxygen, and moisture.

We have now surprisingly and unexpectedly found that atorvastatin can be prepared in crystalline form. Thus, the

2

present invention provides atorvastatin in new crystalline forms designated Form I, Form II, and Form IV. Form I atorvastatin consists of smaller particles and a more uniform size distribution than the previous amorphous product and exhibits more favorable filtration and drying characteristics. Additionally, Form I atorvastatin is purer and more stable than the amorphous product.

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to crystalline Form I atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2θ , d-spacings, and relative intensities with a relative intensity of >20% measured after 2 minutes of grinding and measured on a Siemens D-500 diffractometer with $\text{CuK}\alpha$ radiation:

2θ	d	Relative Intensity (>20%) Ground 2 Minutes
9.150	9.6565	42.60
9.470	9.3311	41.94
10.266	8.6098	55.67
10.560	8.3705	29.33
11.853	7.4601	41.74
12.195	7.2518	24.62
17.075	5.1887	60.12
19.485	4.5520	73.59
21.626	4.1059	100.00
21.960	4.0442	49.44
22.748	3.9059	45.85
23.335	3.8088	44.72
23.734	3.7457	63.04
24.438	3.6394	21.10
28.915	3.0853	23.42
29.234	3.0524	23.36

Further, the present invention is directed to crystalline Form I atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million measured on a Bruker AX-250 spectrometer:

Assignment (7 kHz)	Chemical Shift
C12 or C25	182.8
C12 or C25	178.4
C16	166.7 (broad) and 159.3
<u>Aromatic Carbons</u>	
C2-C5, C13-C18, C19-C24, C27-C32	137.0
	134.9
	131.1
	129.5
	127.6
	123.5
	120.9
	118.2
	113.8
C8, C10	73.1
	70.5
	68.1
	64.9
<u>Methylene Carbons</u>	
C6, C7, C9, C11	47.4
	41.9
	40.2

5,969,156

3

-continued

Assignment (7 kHz)	Chemical Shift
C33	26.4
	25.2
C34	21.3

In a preferred embodiment of the first aspect of the invention, crystalline Form I atorvastatin is a trihydrate.

In a second aspect, the present invention is directed to crystalline Form II atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2 θ , d-spacings, and relative intensities with a relative intensity of >20% measured after 2 minutes of grinding and measured on a Siemens D-500 diffractometer with CuK α radiation:

2 θ	d	Relative Intensity (>20%) Ground 2 Minutes
5.582	15.8180	42.00
7.384	11.9620	38.63
8.533	10.3534	100.00
9.040	9.7741	92.06
12.440 (broad)	7.1094	30.69
15.771 (broad)	5.6146	38.78
17.120–17.360 (broad)	5.1750–5.1040	63.66–55.11
19.490	4.5507	56.64
20.502	4.3283	67.20
22.706–23.159 (broad)	3.9129–3.8375	49.20–48.00
25.697 (broad)	3.4639	38.93
29.504	3.0250	37.86

Further, the second aspect of the present invention is directed to crystalline Form II atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million measured on a Bruker AX-250 spectrometer:

Assignment	Chemical Shift
Spinning Side Band	209.1
Spinning Side Band	206.8
C12 or C25	181 (broad)
C12 or C25	163 (broad)
C16	161 (broad)
<u>Aromatic Carbons</u>	
C2–C5, C13–C18, C19–C24, C27–C32	140.5
	134.8
	133.3
	129.0
	122.9
	121.4
	120.3
	119.0
	117.1
	115.7
	114.7
C8, C10	70.6
	69.0
	68.0
	67.3
Spinning Side Band	49.4
Spinning Side Band	48.9

4

-continued

Assignment	Chemical Shift
<u>Methylene Carbons</u>	
C6, C7, C9, C11	43.4
	42.3
	41.7
	40.2
C33	27.5
C34	22.8 (broad)

In a third aspect, the present invention is directed to crystalline Form IV atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2 θ , d-spacings, and relative intensities with a relative intensity of >15% measured on a Siemens D-500 diffractometer with CuK α radiation:

2 θ	d	Relative Intensity (>15%)
4.889	18.605	38.45
5.424	16.2804	20.12
5.940	14.8660	17.29
7.997	11.0465	100.00
9.680	9.1295	67.31
10.416	8.4859	20.00
12.355	7.1584	19.15
17.662	5.0175	18.57
18.367	4.8265	23.50
19.200	4.6189	18.14
19.569	4.5327	54.79
21.723	4.0879	17.99
23.021	3.8602	28.89
23.651	3.7587	33.39
24.143	3.6832	17.23

Further, the fourth aspect of the present invention is directed to Form IV atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed as parts per million measured on a Bruker AX-250 spectrometer:

Assignment	Chemical Shift
C12 or C25	186.4
	184.9
C12 or C25	181.4
	179.3
C16	166.1 (broad)
	and
	159.0 (broad)
<u>Aromatic Carbons</u>	
C2–C5, C13–C18, C19–C24, C27–C32	138.1 (broad)
	134.7
	129.2
	127.1
	122.7
	119.8
	115.7
C8, C10	71.5
	67.9
	66.3
	63.5
<u>Methylene Carbons</u>	
C6, C7, C9, C11	46.1
	43.4
	42.1

5,969,156

5

-continued

Assignment	Chemical Shift
C33	40.0
C34	25.9
	20.3
	19.4
	17.9

As inhibitors of HMG-CoA, the novel crystalline forms of atorvastatin are useful hypolipidemic and hypocholesterolemic agents.

A still further embodiment of the present invention is a pharmaceutical composition for administering an effective amount of crystalline Form I, Form II, or Form IV atorvastatin in unit dosage form in the treatment methods mentioned above. Finally, the present invention is directed to methods for production of Form I, Form II, or Form IV atorvastatin.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is further described by the following non-limiting examples which refer to the accompanying FIGS. 1 to 6, short particulars of which are given below.

FIG. 1

Diffraction pattern of Form I atorvastatin ground for 2 minutes (Y-axis=0 to maximum intensity of 3767.50 counts per second (cps))

FIG. 2

Diffraction pattern of Form II atorvastatin ground for 2 minutes (Y-axis=0 to maximum intensity of 1500 cps)

FIG. 3

Diffraction pattern of Form IV atorvastatin (Y-axis=0 to maximum intensity of 8212.5 cps).

FIG. 4

Solid-state ^{13}C nuclear magnetic resonance spectrum with spinning side bands identified by an asterisk of Form I atorvastatin.

FIG. 5

Solid-state ^{13}C nuclear magnetic resonance spectrum with spinning side bands identified by an asterisk of Form II atorvastatin.

FIG. 6

Solid-state ^{13}C nuclear magnetic resonance spectrum with spinning side bands identified by an asterisk of Form IV atorvastatin.

DETAILED DESCRIPTION OF THE INVENTION

Crystalline Form I, Form II, or Form IV atorvastatin may be characterized by their X-ray powder diffraction patterns and/or by their solid state nuclear magnetic resonance spectra (NMR).

X-RAY POWDER DIFFRACTION

Forms I, II, and IV Atorvastatin

Forms I, II, or Form IV atorvastatin were characterized by their X-ray powder diffraction pattern. Thus, the X-ray diffraction patterns of Forms I, II, and Form IV atorvastatin were measured on a Siemens D-500 diffractometer with $\text{CuK}\alpha$ radiation.

Equipment

Siemens D-500 Diffractometer-Kristalloflex with an IBM-compatible interface, software=DIFFRAC AT

6

(SOCABIM 1986, 1992). $\text{CuK}\alpha$ radiation (20 mA, 40 kV, $\lambda=1.5406 \text{ \AA}$) Slits I and II at 1°) electronically filtered by the Kevex Psi Peltier Cooled Silicon $[\text{Si}(\text{Li})]$ Detector (Slits: III at 1° and IV at 0.15°).

Methodology

The silicon standard is run each day to check the X-ray tube alignment.

Continuous $\theta/2\theta$ coupled scan: 4.00° to 40.00° in 2θ , scan rate of $6^\circ/\text{min}$: 0.4 sec/ 0.04° step.

Sample tapped out of vial and pressed onto zero-background quartz in aluminum holder. Sample width 13–15 mm.

Samples are stored and run at room temperature.

Grinding/Sieving

Grinding is used to minimize intensity variations for the diffraction pattern disclosed herein. However, if grinding significantly altered the diffraction pattern or increased the amorphous content of the sample, then the diffraction pattern of the unground sample was used. Grinding was done in a small agate mortar and pestle. The mortar was held during the grinding and light pressure was applied to the pestle.

Ground Form II atorvastatin was sieved through a 230 mesh screen before analysis by x-ray diffraction.

Table 1 lists the 2θ , d-spacings, and relative intensities of all lines in the unground sample with a relative intensity of $>20\%$ for crystalline Form I atorvastatin. Table 1 also lists the relative intensities of the same lines in a diffraction pattern measured after 2 minutes of grinding. The intensities of the sample ground for 2 minutes are more representative of the diffraction pattern without preferred orientation. It should also be noted that the computer-generated, unrounded numbers are listed in this table.

TABLE 1

Intensities and Peak Locations of all Diffraction Lines With Relative Intensity Greater Than 20% for Form I Atorvastatin				
			Relative Intensity ($>20\%$) No Grinding	Relative Intensity ($>20\%$)* Ground 2 Minutes
2θ	d			
9.150	9.6565		37.42	42.60
9.470	9.3311		46.81	41.94
10.266	8.6098		75.61	55.67
10.560	8.3705		24.03	29.33
11.853	7.4601		55.16	41.74
12.195	7.2518		20.03	24.62
17.075	5.1887		25.95	60.12
19.485	4.5520		89.93	73.59
21.626	4.1059		100.00	100.00
21.960	4.0442		58.64	49.44
22.748	3.9059		36.95	45.85
23.335	3.8088		31.76	44.72
23.734	3.7457		87.55	63.04
24.438	3.6394		23.14	21.10
28.915	3.0853		21.59	23.42
29.234	3.0524		20.45	23.36

*The second relative intensity column gives the relative intensities of the diffraction lines on the original diffraction pattern after 2 minutes of grinding.

Table 2 lists the 2θ , d-spacings, and relative intensities of all lines in the ground/sieved sample with a relative intensity of $>20\%$ for crystalline Form II atorvastatin. It should also be noted that the computer-generated unrounded numbers are listed in this table.

5,969,156

7

8

TABLE 2

Intensities and Peak Locations of All Diffraction Lines With Relative Intensity Greater Than 20% for Form II Atorvastatin		
2 θ	d	Relative Intensity (>20%)
5.582	15.8180	42.00
7.384	11.9620	38.63
8.533	10.3534	100.00
9.040	9.7741	92.06
12.440 (broad)	7.1094	30.69
15.771 (broad)	5.6146	38.78
17.120–17.360 (broad)	5.1750–5.1040	63.66–55.11
19.490	4.5507	56.64
20.502	4.3283	67.20
22.706–23.159 (broad)	3.9129–3.8375	49.20–48.00
25.697 (broad)	3.4639	38.93
29.504	3.0250	37.86

5

10

15

20

Table 3 lists the 2 θ , d-spacings, and relative intensities of all lines in the unground sample with a relative intensity of >15% for crystalline Form IV atorvastatin. It should also be noted that the computer-generated unrounded numbers are listed in this table.

TABLE 3

Intensities and Peak Locations of All Diffraction Lines With Relative Intensity Greater Than 15% for Form IV Atorvastatin		
2 θ	d	Relative Intensity (>15%)
4.889	18.605	38.45
5.424	16.2804	20.12
5.940	14.8660	17.29
7.997	11.0465	100.00

25

30

35

TABLE 3-continued

Intensities and Peak Locations of All Diffraction Lines With Relative Intensity Greater Than 15% for Form IV Atorvastatin		
2 θ	d	Relative Intensity (>15%)
9.680	9.1295	67.31
10.416	8.4859	20.00
12.355	7.1584	19.15
17.662	5.0175	18.57
18.367	4.8265	23.50
19.200	4.6189	18.14
19.569	4.5327	54.79
21.723	4.0879	17.99
23.021	3.8602	28.89
23.651	3.7587	33.39
24.143	3.6832	17.23

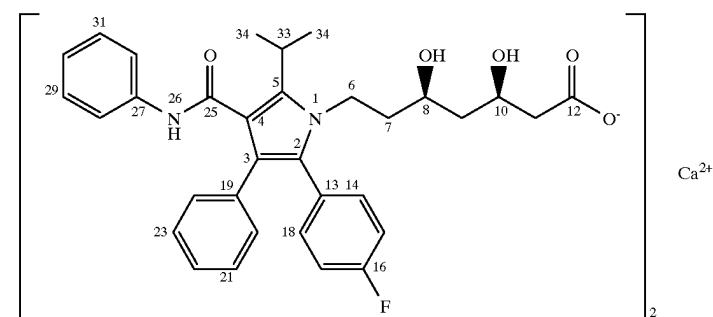
SOLID STATE NUCLEAR MAGNETIC RESONANCE (NMR)

Methodology

All solid-state ^{13}C NMR measurements were made with a Bruker AX-250, 250 MHz NMR spectrometer. High resolution spectra were obtained using high-power proton decoupling and cross-polarization (CP) with magic-angle spinning (MAS) at approximately 5 kHz. The magic-angle was adjusted using the Br signal of KBr by detecting the side bands as described by Frye and Maciel (Frye J. S. and Maciel G. E., *J. Mag. Res.*, 1982;48:125). Approximately 300 to 450 mg of sample packed into a canister-design rotor was used for each experiment. Chemical shifts were referenced to external tetrakis (trimethylsilyl)silane (methyl signal at 3.50 ppm) (Muntean J. V. and Stock L. M., *J. Mag. Res.*, 1988;76:54).

Table 4 shows the solid-state NMR spectrum for crystalline Form I atorvastatin.

TABLE 4



Carbon Atom Assignment and Chemical
Shift for Form I Atorvastatin

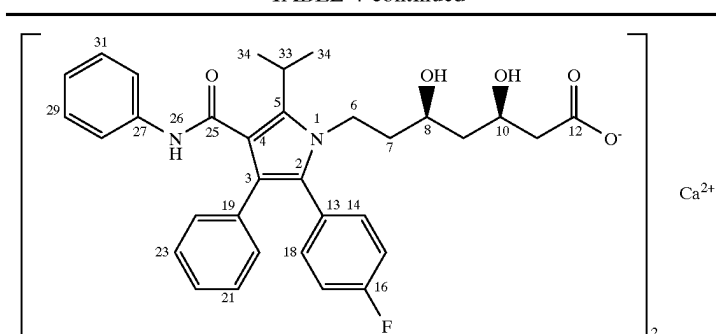
Assignment (7 kHz)	Chemical Shift
C12 or C25	182.8
C12 or C25	178.4
C16	166.7 (broad) and 159.3
Aromatic Carbons	137.0
C2–C5, C13–C18, C19–C24, C27–C32	134.9
	131.1

5,969,156

9

10

TABLE 4-continued



Carbon Atom Assignment and Chemical Shift for Form I Atorvastatin

Assignment (7 kHz)	Chemical Shift
	129.5
	127.6
	123.5
	120.9
	118.2
	113.8
C8, C10	73.1
	70.5
	68.1
	64.9
Methylene Carbons C6, C7, C9, C11	47.4
	41.9
	40.2
C33	26.4
	25.2
C34	21.3

Table 5 shows the solid-state NMR spectrum for crystalline Form II atorvastatin.

TABLE 5

Carbon Atom Assignment and Chemical Shift for Form II Atorvastatin		
Assignment	Chemical Shift	
Spinning Side Band	209.1	40
Spinning Side Band	206.8	
C12 or C25	181 (broad)	
C12 or C25	163 (broad)	
C16	161 (broad)	
<u>Aromatic Carbons</u>		50
C2-C5, C13-C18, C19-C24, C27-C32	140.5	
	134.8	
	133.3	
	129.0	
	122.9	55
	121.4	
	120.3	
	119.0	
	117.1	
	115.7	
	114.7	
	70.6	
C8, C10	69.0	
	68.0	
	67.3	
Spinning Side Band	49.4	60
Spinning Side Band	48.9	

TABLE 5-continued

Carbon Atom Assignment and Chemical Shift for Form II Atorvastatin	
Assignment	Chemical Shift
<u>Methylene Carbons</u>	
C6, C7, C9, C11	43.4
	42.3
	41.7
	40.2
C33	27.5
C34	22.8 (broad)

Table 6 shows the solid-state NMR spectrum for crystalline Form IV atorvastatin.

TABLE 6

Carbon Atom Assignment and Chemical Shift for Form IV Atorvastatin	
Assignment	Chemical Shift
C12 or C25	186.4
	184.9
C12 or C25	181.4
	179.3
C16	166.1 (broad) and 159.0 (broad)

5,969,156

11

TABLE 6-continued

Carbon Atom Assignment and Chemical Shift for Form IV Atorvastatin	
Assignment	Chemical Shift
<u>Aromatic Carbons</u>	
C2-C5, C13-C18, C19-C24, C27-C32	138.1 (broad)
	134.7
	129.2
	127.1
	122.7
	119.8
	115.7
C8, C10	71.5
	67.9
	66.3
	63.5
<u>Methylene Carbons</u>	
C6, C7, C9, C11	46.1
	43.4
	42.1
	40.0
C33	25.9
C34	20.3
	19.4
	17.9

Crystalline Form I, Form II, and Form IV atorvastatin of the present invention may exist in anhydrous forms as well as hydrated forms. In general, the hydrated forms, are equivalent to unhydrated forms and are intended to be encompassed within the scope of the present invention. Crystalline Form I atorvastatin contains about 1 to 8 mol of water. Preferably, Form I atorvastatin contains 3 mol of water.

The present invention provides a process for the preparation of crystalline Form I atorvastatin which comprises crystallizing atorvastatin from a solution in solvents under conditions which yield crystalline Form I atorvastatin.

The precise conditions under which crystalline Form I atorvastatin is formed may be empirically determined and it is only possible to give a number of methods which have been found to be suitable in practice.

Thus, for example, crystalline Form I atorvastatin may be prepared by crystallization under controlled conditions. In particular, it can be prepared either from an aqueous solution of the corresponding basic salt such as, an alkali metal salt, for example, lithium, potassium, sodium, and the like; ammonia or an amine salt; preferably, the sodium salt by addition of a calcium salt, such as, for example, calcium acetate and the like, or by suspending amorphous atorvastatin in water. In general, the use of a hydroxylic co-solvent such as, for example, a lower alkanol, for example methanol and the like, is preferred.

When the starting material for the preparation of the desired crystalline Form I atorvastatin is a solution of the corresponding sodium salt, one preferred preparation involves treating a solution of the sodium salt in water containing not less than about 5% v/v methanol, preferably about 5% to 33% v/v methanol, particularly preferred about 10% to 15% v/v methanol, with an aqueous solution of calcium acetate, preferably at an elevated temperature at up to about 70° C. such as, for example, about 45–60° C., particularly preferred about 47–52° C. It is preferable to use calcium acetate and, in general, 1 mole of calcium acetate to 2 moles of the sodium salt of atorvastatin. Under these conditions, calcium salt formation as well as crystallization should preferably be carried out at an elevated temperature,

12

for example within the above-mentioned temperature ranges. It has been found that it may be advantageous to include in the starting solution a small amount of methyl tert-butyl ether (MTBE) such as, for example, about 7% w/w. It has frequently been found desirable to add “seeds” of crystalline Form I atorvastatin to the crystallization solution in order to consistently produce crystalline Form I atorvastatin.

When the starting material is amorphous atorvastatin or a combination of amorphous and crystalline Form I Atorvastatin, the desired crystalline Form I atorvastatin may be obtained by suspending the solid in water containing up to about 40% v/v, such as, for example, about 0% to 20% v/v, particularly preferred about 5% to 15% v/v co-solvent such as, for example, methanol, ethanol, 2-propanol, acetone, and the like until conversion to the required form is complete, followed by filtration. It has frequently been found desirable to add “seeds” of crystalline Form I atorvastatin to the suspension in order to ensure complete conversion to crystalline Form I atorvastatin. Alternatively, a water-wet cake consisting principally of amorphous atorvastatin can be heated at elevated temperatures such as, for example, up to about 75° C., particularly preferred about 65–70° C., until a significant amount of crystalline Form I atorvastatin is present, whereupon the amorphous/crystalline Form I mixture can be slurried as described above.

Crystalline Form I atorvastatin is significantly easier to isolate than amorphous atorvastatin and can be filtered from the crystallization medium after cooling, and washed and dried. For example, filtration of a 50 mL slurry of crystalline Form I atorvastatin was complete within 10 seconds. A similarly sized sample of amorphous atorvastatin took more than an hour to filter.

The present invention also provides a process for the preparation of crystalline Form II atorvastatin which comprises suspending atorvastatin in solvents under conditions which yield crystalline Form II atorvastatin.

The precise conditions under which Form II of crystalline atorvastatin is formed may be empirically determined and it is only possible to give a method which has been found to be suitable in practice.

Thus, for example, when the starting material is amorphous, a combination of amorphous and Form I, or crystalline Form I atorvastatin, the desired Form II of crystalline atorvastatin may be obtained by suspending the solid in methanol containing about 40% to about 50% water until conversion to the required form is complete, followed by filtration.

The present invention also provides a process for the preparation of crystalline Form IV atorvastatin which comprises crystallizing atorvastatin from a solution thereof in solvents under conditions which yield crystalline Form IV atorvastatin.

The precise conditions under which Form IV of crystalline atorvastatin is formed may be empirically determined and it is only possible to give a method which has been found to be suitable in practice.

Thus, for example, when the starting material is Form I of crystalline atorvastatin, the desired Form IV of crystalline atorvastatin may be obtained by dissolving the solid in methanol whereupon crystalline Form IV precipitates.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously,

5,969,156

13

intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either compounds or a corresponding pharmaceutically acceptable salt of a compound of the present invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from two or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, retention enemas, and emulsions, for example water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active

14

component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.5 mg to 100 mg, preferably 2.5 mg to 80 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as hypolipidemic and/or hypocholesterolemic agents, the crystalline Forms I, II, and Form IV atorvastatin utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 2.5 mg to about 80 mg daily. A daily dose range of about 2.5 mg to about 20 mg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

EXAMPLE 1

[R-(R*,R*)]-2-(4-Fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form I Atorvastatin)

Method A

A mixture of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (atorvastatin lactone) (U.S. Pat. No. 5,273,995) (75 kg), methyl tertiary-butyl ether (MTBE) (308 kg), methanol (190 L) is reacted with an aqueous solution of sodium hydroxide (5.72 kg in 950 L) at 48–58° C. for 40 to 60 minutes to form the ring-opened sodium salt. After cooling to 25–35° C., the organic layer is discarded, and the aqueous layer is again extracted with MTBE (230 kg). The organic layer is discarded, and the MTBE saturated aqueous solution of the sodium salt is heated to 47–52° C. To this solution is added a solution of calcium acetate hemihydrate (11.94 kg) dissolved in water (410 L), over at least 30 minutes. The mixture is seeded with a slurry of crystalline Form I atorvastatin (1.1 kg in 11 L water and 5 L methanol) shortly after addition of the calcium acetate solution. The mixture is then heated to 51–57° C. for at least 10 minutes and then cooled to 15–40° C. The mixture is filtered, washed with a solution of water (300 L) and methanol (150 L) followed by water (450 L). The solid is dried at 60–70° C. under vacuum for 3 to 4 days to give crystalline Form I atorvastatin (72.2 kg).

Method B

Amorphous atorvastatin (9 g) and crystalline Form I atorvastatin (1 g) are stirred at about 40° C. in a mixture of water (170 mL) and methanol (30 mL) for a total of 17 hours. The mixture is filtered, rinsed with water, and dried at 70° C. under reduced pressure to give crystalline Form I atorvastatin (9.7 g).

5,969,156

15

EXAMPLE 2

[R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt
(Form II Atorvastatin)

A mixture of amorphous and crystalline Form I atorvastatin (100 g) was suspended in a mixture of methanol (1200 mL) and water (800 mL) and stirred for 3 days. The material was filtered, dried at 70° C. under reduced pressure to give crystalline Form II atorvastatin.

EXAMPLE 3

[R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt
(Form IV Atorvastatin)

A mixture of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (atorvastatin lactone) (U.S. Pat. No. 5,273,995) (12 kg), MTBE (50 kg), methanol (30 L) is reacted with an aqueous solution of sodium hydroxide (1.83 kg in 150 L) at 50–55° C. for 30–45 minutes to form the ring-opened sodium salt. After cooling to 20–25° C., the organic layer is discarded and the aqueous layer is again extracted with MTBE (37 kg). The organic layer is discarded and the aqueous solution of the sodium salt is heated to 70–80° C. and the residual MTBE is removed by distillation. The solution is then cooled to 60–70° C. To this solution is added a solution of calcium acetate hemihydrate (1.91 kg) dissolved in water/methanol (72 L water+16 L methanol). The mixture is seeded with crystalline Form I atorvastatin (180 g) shortly after addition of the calcium acetate solution. The mixture is heated at 65–75° C. for at least 5 minutes and then cooled to 50–55° C. The mixture is filtered and slurried in methanol (about 200 L) at 55–65° C. and then cooled to 25–30° C. and filtered. The solid is dried at 66–70° C. under vacuum to give Form IV of crystalline atorvastatin (about 3 kg isolated).

We claim:

1. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing at least one of the following 2 θ values measured using CuK α radiation: 11.9 or 22.0.
2. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2 θ values measured using CuK α radiation: 11.9, 21.6 and 22.0.
3. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2 θ values measured using CuK α radiation: 17.1, 19.5 and 21.6.
4. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2 θ values measured using CuK α radiation: 9.2, 9.5, 10.3, 10.6, 11.9, 12.2, 17.1, 19.5, 21.6, 22.0, 22.7, 23.3, 23.7, 24.4, 28.9 and 29.2.
5. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2 θ values measured using CuK α radiation: 9.150, 9.470, 10.266, 10.560, 11.853, 12.195, 17.075, 19.485, 21.626, 21.960, 22.748, 23.335, 23.734, 24.438, 28.915 and 29.234.
6. A crystalline Form I atorvastatin hydrate characterized by solid state ^{13}C nuclear magnetic resonance having a chemical shift difference between the lowest ppm resonance and another resonance of 5.1 or 51.8.
7. A crystalline Form I atorvastatin hydrate characterized by solid state ^{13}C nuclear magnetic resonance and having

16

the following chemical shift differences between the lowest ppm resonance and other resonances: 3.9, 5.1, 43.6, 46.8, 49.2 and 51.8.

8. A crystalline Form I atorvastatin hydrate characterized by solid-state ^{13}C nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 3.9, 5.1, 18.9, 20.6, 26.1, 43.6, 46.8, 49.2, 51.8, 92.5, 96.9, 99.6, 102.2, 106.3, 108.2, 109.8, 113.6, 115.7, 138.0, 145.4, 157.1 and 161.5.

9. A crystalline Form I atorvastatin hydrate characterized by solid-state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 21.3, 25.2, 26.4, 40.2, 41.9, 47.4, 64.9, 68.1, 70.5, 73.1, 113.8, 118.2, 120.9, 123.5, 127.6, 129.5, 131.1, 134.9, 137.0, 159.3, 166.7 (broad), 178.4 and 182.8.

10. The crystalline Form I atorvastatin hydrate of claim 1 containing about 1 to 8 moles of water.

11. The crystalline Form I atorvastatin hydrate of claim 1 containing 3 moles of water.

12. The crystalline Form I atorvastatin hydrate of claim 2 containing about 1 to 8 moles of water.

13. The crystalline Form I atorvastatin hydrate of claim 2 containing 3 moles of water.

14. The crystalline Form I atorvastatin hydrate of claim 3 containing about 1 to 8 moles of water.

15. The crystalline Form I atorvastatin hydrate of claim 3 containing 3 moles of water.

16. The crystalline Form I atorvastatin hydrate of claim 4 containing about 1 to 8 moles of water.

17. The crystalline Form I atorvastatin hydrate of claim 4 containing 3 moles of water.

18. The crystalline Form I atorvastatin hydrate of claim 5 containing about 1 to 8 moles of water.

19. The crystalline Form I atorvastatin hydrate of claim 5 containing 3 moles of water.

20. The crystalline Form I atorvastatin hydrate of claim 6 containing about 1 to 8 moles of water.

21. The crystalline Form I atorvastatin hydrate of claim 6 containing 3 moles of water.

22. The crystalline Form I atorvastatin hydrate of claim 7 containing about 1 to 8 moles of water.

23. The crystalline Form I atorvastatin hydrate of claim 7 containing 3 moles of water.

24. The crystalline Form I atorvastatin hydrate of claim 8 containing about 1 to 8 moles of water.

25. The crystalline Form I atorvastatin hydrate of claim 8 containing 3 moles of water.

26. The crystalline Form I atorvastatin hydrate of claim 9 containing about 1 to 8 moles of water.

27. The crystalline Form I atorvastatin hydrate of claim 9 containing 3 moles of water.

28. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2 θ values measured using CuK α radiation: 9.0 and 20.5.

29. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2 θ values measured using CuK α radiation: 8.5 and 9.0.

30. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2 θ values measured using CuK α radiation: 5.6, 7.4, 8.5, 9.0, 12.4 (broad), 15.8 (broad), 17.1–17.4 (broad), 19.5, 20.5, 22.7–23.2 (broad), 25.7 (broad) and 29.5.

31. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2 θ values measured using CuK α radiation: 5.582, 7.384, 8.533, 9.040, 12.440 (broad), 15.771 (broad), 17.120–17.360 (broad), 19.490, 20.502, 22.706–23.159 (broad), 25.697 (broad) and 29.504.

5,969,156

17

32. Crystalline Form II atorvastatin or a hydrate thereof characterized by solid state ^{13}C nuclear magnetic resonance having a chemical shift difference between the lowest ppm resonance and another resonance of 4.7 or 47.8.

33. Crystalline Form II atorvastatin or a hydrate thereof characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 4.7, 44.5, 45.2, 46.2 and 47.8.

34. Crystalline Form II atorvastatin or a hydrate thereof characterized by solid-state ^{13}C nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 4.7, 17.4, 18.9, 19.5, 20.6, 44.5, 45.2, 46.2, 47.8, 91.9, 92.9, 94.3, 96.2, 97.5, 98.6, 100.1, 106.2, 110.5, 112.0, 117.7, 138.2, 140.2 and 158.2.

35. Crystalline Form II atorvastatin or a hydrate thereof characterized by solid-state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 22.8 (broad), 27.5, 40.2, 41.7, 42.3, 43.4, 67.3, 68.0, 69.0, 70.6, 114.7, 115.7, 117.1, 119.0, 120.3, 121.4, 122.9, 129.0, 133.3, 134.8, 140.5, 161 (broad), 163 (broad) and 181 (broad).

36. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing at least one of the following 2 θ values measured using $\text{CuK}\alpha$ radiation: 8.0 or 9.7.

37. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2 θ values measured using $\text{CuK}\alpha$ radiation: 4.9, 8.0 and 9.7.

38. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2 θ values measured using $\text{CuK}\alpha$ radiation: 8.0, 9.7 and 19.6.

39. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following

18

2 θ values measured using $\text{CuK}\alpha$ radiation: 4.9, 5.4, 5.9, 8.0, 9.7, 10.4, 12.4, 17.7, 18.4, 19.2, 19.6, 21.7, 23.0, 23.7 and 24.1.

40. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2 θ values measured using $\text{CuK}\alpha$ radiation: 4.889, 5.424, 5.940, 7.997, 9.680, 10.416, 12.355, 17.662, 18.367, 19.200, 19.569, 21.723, 23.021, 23.651 and 24.143.

41. Crystalline Form IV atorvastatin or a hydrate thereof characterized by solid state ^{13}C nuclear magnetic resonance having a chemical shift difference between the lowest ppm resonance and another resonance of 8.0 or 53.6.

42. Crystalline Form IV atorvastatin or a hydrate thereof characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 1.5, 2.4, 8.0, 45.6, 48.4, 50.0 and 53.6.

43. Crystalline Form IV atorvastatin or a hydrate thereof characterized by solid-state ^{13}C nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 1.5, 2.4, 8.0, 22.1, 24.2, 25.5, 28.2, 45.6, 48.4, 50.0, 53.6, 97.8, 101.9, 104.8, 109.2, 111.3, 116.8, 120.2, 141.1, 148.2, 161.4, 163.5, 167.0 and 168.5.

44. Crystalline Form IV atorvastatin or a hydrate thereof characterized by solid-state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 17.9, 19.4, 20.3, 25.9, 40.0, 42.1, 43.4, 46.1, 63.5, 66.3, 67.9, 71.5, 115.7, 119.8, 122.7, 127.1, 129.2, 134.7, 138.1 (broad), 159.0 (broad), 166.1 (broad), 179.3, 181.4, 184.9 and 186.4.

* * * * *

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- (54) **CRYSTALLINE [R-(R*,R*)]-2-(4-FLUOROPHENYL)- β , δ -DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID HEMI-CALCIUM SALT (ATORVASTATIN)**
- (75) **Inventors: Christopher A. Briggs, Holland, MI (US); Rex A. Jennings, Holland, MI (US); Robert Wade, Holland, MI (US); Kikuko Harasawa, Sagamihara (JP); Shigeru Ichikawa, Machida (JP); Kazuo Minohara, Sagamihara (JP); Shinsuke Nakagawa, Sagamihara (JP)**
- (73) **Assignee: Warner-Lambert Company, Morris Plains, NJ (US)**

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(57) **ABSTRACT**

Crystalline forms of atorvastatin and hydrates thereof are useful hypolipidemic and hypocholesterolemic agents.

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US 5,969,156 C1

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US 5,969,156 C1

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US 5,969,156 C1

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US 5,969,156 C1

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US 5,969,156 C1

1
EX PARTE
REEXAMINATION CERTIFICATE
ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS
INDICATED BELOW.

Matter enclosed in heavy brackets [] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

The patentability of claims 3, 6–8, 14–15, 20–25, 30, 32–35, 37 and 39–44 is confirmed.

Claims 1–2, 4–5, 9, 28–29, 31, 36 and 38 are determined to be patentable as amended.

Claims 10–13, 16–19 and 26–27, dependent on an amended claim, are determined to be patentable.

New claims 45–117 are added and determined to be patentable.

1. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing [at least one of] the following 2θ [values] value measured using CuK_α radiation: [11.9 or] 22.0.

2. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using [CuK_α] CuK_α radiation: 11.9, 21.6 and 22.0.

4. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using [CuK_α] CuK_α radiation: 9.2, 9.5, 10.3, 10.6, 11.9, 12.2, 17.1, 19.5, 21.6, 22.0, 22.7, 23.3, 23.7, 24.4, 28.9 and 29.2.

5. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using [CuK_α] CuK_α radiation: 9.150, 9.470, 10.266, 10.560, 11.853, 12.195, 17.075, 19.485, 21.626, 21.960, 22.748, 23.335, 23.734, 24.438, 28.915 and 29.234.

9. A crystalline Form I atorvastatin hydrate characterized by solid-state ¹³C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 21.3[.], 25.2, 26.4, 40.2, 41.9, 47.4, 64.9, 68.1, 70.5, 73.1, 113.8, 118.2, 120.9, 123.5, 127.6, 129.5, 131.1, 134.9, 137.0, 159.3, 166.7, (broad), 178.4 and 182.8.

28. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 9.0 [and], 20.5 and at least one value selected from the group consisting of 5.6, 7.4, 8.5, 15.8 (broad) and 25.7 (broad).

29. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 8.5 [and], 9.0 and at least one value selected from the group consisting of 7.4, 12.4 (broad), 15.8 (broad), 17.1–17.4 (broad), 19.5, 20.5, 22.7–23.2 (broad) and 25.7 (broad).

2

31. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using [CuK_α] CuK_α radiation: 5.582, 7.384, 8.533, 9.040, 12.440 (broad), 15.771 (broad), 17.120–17.360 (broad), 19.490, 20.502, 22.706–23.159 (broad), 25.697 (broad) and 29.504.

36. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing [at least one of] the following 2θ values measured using CuK_α radiation: 8.0 [or], 9.7 and at least one value selected from the group consisting of 4.9, 5.4, 10.4, 12.4, 18.4, 19.2, 21.7, 23.0 and 24.1.

38. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 8.0, 9.7 [and], 19.6 and at least one value selected from the group consisting of 4.9, 5.4, 10.4, 12.4, 18.4, 19.2, 21.7, 23.0 and 24.1.

45. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 11.9 and 22.0.

46. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 8.0 and at least one value selected from the group consisting of 4.9, 5.4, 10.4, 12.4, 18.4, 19.2, 21.7, 23.0 and 24.1.

47. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 17.1, 19.5, 21.6 and at least one value selected from the group consisting of 9.2, 10.3, 11.9, 12.2, 22.0, 22.7, 23.7, 24.4, 28.9 and 29.2.

48. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 8.0 and 12.4.

49. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 8.0, 9.7 and 12.4.

50. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 4.9, 8.0, 9.7 and at least one value selected from the group consisting of 5.4, 5.9, 10.4, 12.4, 17.7, 19.6 and 23.7.

51. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 8.0, 9.7, 19.6 and at least one value selected from the group consisting of 4.9, 12.4 and 21.7.

52. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 9.2, 9.5, 10.3, 10.6 and 22.0.

53. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 9.2, 9.5, 10.3, 10.6 and 11.9.

54. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using CuK_α radiation: 9.2, 9.5, 10.3, 10.6, 11.9, 21.6 and 22.0.

US 5,969,156 C1

3

55. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using $\text{CuK}\alpha$ radiation: 9.2, 9.5, 10.3, 10.6, 17.1, 19.5 and 21.6.

56. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $\text{CuK}\alpha$ radiation: 5.6, 8.5, 9.0, 12.4 (broad), 17.1–17.4 (broad) and 20.5.

57. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $\text{CuK}\alpha$ radiation: 5.6, 8.5, 9.0, 12.4 (broad) and 17.1–17.4 (broad).

58. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $\text{CuK}\alpha$ radiation: 4.9, 8.0, 9.7 and 12.4.

59. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $\text{CuK}\alpha$ radiation: 4.9, 8.0, 9.7, 12.4 and at least one value selected from the group consisting of 5.4, 5.9, 10.4, 17.7, 18.4, 19.2, 19.6, 21.7, 23.0, 23.7 and 24.1.

60. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $\text{CuK}\alpha$ radiation: 4.9, 8.0, 9.7, 12.4 and 19.6.

61. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ value measured using $\text{CuK}\alpha$ radiation: 11.9; and further characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 3.9, 5.1, 43.6, 46.8, 49.2 and 51.8.

62. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ value measured using $\text{CuK}\alpha$ radiation: 22.0; and further characterized by solid state ^{13}C nuclear magnetic resonance having a chemical shift difference between the lowest ppm resonance and another resonance of 5.1.

63. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ value measured using $\text{CuK}\alpha$ radiation: 22.0; and further characterized by solid state ^{13}C nuclear magnetic resonance having a chemical shift difference between the lowest ppm resonance and another resonance of 51.8.

64. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ value measured using $\text{CuK}\alpha$ radiation: 22.0; and further characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 3.9, 5.1, 43.6, 46.8, 49.2 and 51.8.

65. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using $\text{CuK}\alpha$ radiation: 9.2 and 11.9; and further characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shift expressed in parts per million: 182.8.

4

66. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using $\text{CuK}\alpha$ radiation: 9.2 and 22.0; and further characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shift expressed in parts per million: 182.8.

67. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ value measured using $\text{CuK}\alpha$ radiation: 11.9; and further characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 21.3, 25.2, 26.4, 40.2, 41.9, 47.4, 64.9, 68.1, 70.5, 73.1, 113.8, 118.2, 120.9, 123.5, 127.6, 129.5, 131.1, 134.9, 137.0, 159.3, 166.7 (broad), 178.4 and 182.8.

68. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ value measured using $\text{CuK}\alpha$ radiation: 22.0; and further characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 21.3, 25.2, 26.4, 40.2, 41.9, 47.4, 64.9, 68.1, 70.5, 73.1, 113.8, 118.2, 120.9, 123.5, 127.6, 129.5, 131.1, 134.9, 137.0, 159.3, 166.7 (broad), 178.4 and 182.8.

69. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using $\text{CuK}\alpha$ radiation: 11.9 and 22.0; and further characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 21.3, 25.2, 26.4, 40.2, 41.9, 47.4, 64.9, 68.1, 70.5, 73.1, 113.8, 118.2, 120.9, 123.5, 127.6, 129.5, 131.1, 134.9, 137.0, 159.3, 166.7 (broad), 178.4 and 182.8.

70. The crystalline Form I atorvastatin hydrate of claim 45 containing about 1 to 8 moles of water.

71. The crystalline Form I atorvastatin hydrate of claim 47 containing about 1 to 8 moles of water.

72. The crystalline Form I atorvastatin hydrate of claim 52 containing about 1 to 8 moles of water.

73. The crystalline Form I atorvastatin hydrate of claim 53 containing about 1 to 8 moles of water.

74. The crystalline Form I atorvastatin hydrate of claim 54 containing about 1 to 8 moles of water.

75. The crystalline Form I atorvastatin hydrate of claim 55 containing about 1 to 8 moles of water.

76. The crystalline Form I atorvastatin hydrate of claim 61 containing about 1 to 8 moles of water.

77. The crystalline Form I atorvastatin hydrate of claim 62 containing about 1 to 8 moles of water.

78. The crystalline Form I atorvastatin hydrate of claim 63 containing about 1 to 8 moles of water.

79. The crystalline Form I atorvastatin hydrate of claim 64 containing about 1 to 8 moles of water.

80. The crystalline Form I atorvastatin hydrate of claim 65 containing about 1 to 8 moles of water.

81. The crystalline Form I atorvastatin hydrate of claim 66 containing about 1 to 8 moles of water.

US 5,969,156 C1

5

82. The crystalline Form I atorvastatin hydrate of claim 67 containing about 1 to 8 moles of water.

83. The crystalline Form I atorvastatin hydrate of claim 68 containing about 1 to 8 moles of water.

84. The crystalline Form I atorvastatin hydrate of claim 69 containing about 1 to 8 moles of water.

85. The crystalline Form I atorvastatin hydrate of claim 45 containing 3 moles of water.

86. The crystalline Form I atorvastatin hydrate of claim 47 containing 3 moles of water.

87. The crystalline Form I atorvastatin hydrate of claim 52 containing 3 moles of water.

88. The crystalline Form I atorvastatin hydrate of claim 53 containing 3 moles of water.

89. The crystalline Form I atorvastatin hydrate of claim 54 containing 3 moles of water.

90. The crystalline Form I atorvastatin hydrate of claim 55 containing 3 moles of water.

91. The crystalline Form I atorvastatin hydrate of claim 61 containing 3 moles of water.

92. The crystalline Form I atorvastatin hydrate of claim 62 containing 3 moles of water.

93. The crystalline Form I atorvastatin hydrate of claim 63 containing 3 moles of water.

94. The crystalline Form I atorvastatin hydrate of claim 64 containing 3 moles of water.

95. The crystalline Form I atorvastatin hydrate of claim 65 containing 3 moles of water.

96. The crystalline Form I atorvastatin hydrate of claim 66 containing 3 moles of water.

97. The crystalline Form I atorvastatin hydrate of claim 67 containing 3 moles of water.

98. The crystalline Form I atorvastatin hydrate of claim 68 containing 3 moles of water.

99. The crystalline Form I atorvastatin hydrate of claim 69 containing 3 moles of water.

100. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2 θ values measured using CuK α radiation: 9.0, 20.5 and at least one value selected from the group consisting of 5.6, 7.4, 8.5, 15.8 (broad) and 25.7 (broad); and further characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shift difference between the lowest ppm resonance and another resonance of 4.7.

101. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2 θ values measured using CuK α radiation: 9.0, 20.5 and at least one value selected from the group consisting of 5.6, 7.4,

6

8.5, 15.8 (broad) and 25.7 (broad); and further characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shift difference between the lowest ppm resonance and another resonance of 47.8.

102. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2 θ values measured using CuK α radiation: 9.0, 20.5 and at least one value selected from the group consisting of 5.6, 7.4, 8.5, 15.8 (broad) and 25.7 (broad); and further characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 4.7, 44.5, 45.2, 46.2 and 47.8.

103. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2 θ values measured using CuK α radiation: 9.0, 20.5 and at least one value selected from the group consisting of 5.6, 7.4, 8.5, 15.8 (broad) and 25.7 (broad); and further characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 22.8 (broad), 27.5, 40.2, 41.7, 42.3, 43.4, 67.3, 68.0, 69.0, 70.6, 114.7, 115.7, 117.1, 119.0, 120.3, 121.4, 122.9, 129.0, 133.3, 134.8, 140.5, 161 (broad), 163 (broad) and 181 (broad).

104. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2 θ values measured using CuK α radiation: 8.5 and 9.0; and further characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 140.5 and 181 (broad).

105. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2 θ values measured using CuK α radiation: 8.5, 9.0 and at least one value selected from the group consisting of 7.4, 12.4, (broad), 15.8 (broad), 17.1–17.4 (broad), 19.5, 20.5, 22.7–23.2 (broad) and 25.7 (broad); and further characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 140.5 and 181 (broad).

106. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2 θ value measured using CuK α radiation: 8.0; and further characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 127.1, 184.9 and 186.4.

107. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2 θ values measured using CuK α radiation: 8.0 and 9.7; and further characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 127.1, 184.9 and 186.4.

108. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2 θ values measured using CuK α radiation: 4.9, 8.0 and 9.7; and further characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 127.1, 184.9 and 186.4.

109. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2 θ values measured using CuK α radiation: 8.0,

US 5,969,156 C1

7

9.7 and 19.6; and further characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 127.1, 184.9 and 186.4.

110. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using $\text{CuK}\alpha$ radiation: 9.2, 9.5, 10.3, 10.6, 11.9, 12.2, 17.1, 19.5, 21.6, 22.0, 22.7, 23.3, 23.7, 24.4, 28.9 and 29.2; and further characterized by solid-state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 21.3, 25.2, 26.4, 40.2, 41.9, 47.4, 64.9, 68.1, 70.5, 73.1, 113.8, 118.2, 120.9, 123.5, 127.6, 129.5, 131.1, 134.9, 137.0, 159.3, 166.7 (broad), 178.4 and 182.8.

111. The crystalline Form I atorvastatin hydrate of claim 110 containing about 1 to 8 moles of water.

112. The crystalline Form I atorvastatin hydrate of claim 110 containing 3 moles of water.

113. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $\text{CuK}\alpha$ radiation: 5.6, 7.4, 8.5, 9.0, 12.4 (broad), 15.8 (broad), 17.1–17.4 (broad), 19.5, 20.5, 22.7–23.2 (broad), 25.7 (broad) and 29.5; and further characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 22.8 (broad), 27.5, 40.2, 41.7, 42.3, 43.4, 67.3, 68.0, 69.0, 70.6, 114.7, 115.7, 117.1, 119.0, 120.3, 121.4, 122.9, 129.0, 133.3, 134.8, 140.5, 161 (broad), 163 (broad) and 181 (broad).

8

114. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $\text{CuK}\alpha$ radiation: 4.9, 5.4, 5.9, 8.0, 9.7, 10.4, 12.4, 17.7, 18.4, 19.2, 19.6, 21.7, 23.0, 23.7 and 24.1; and further characterized by solid state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 17.9, 19.4, 20.3, 25.9, 40.0, 42.1, 43.4, 46.1, 63.5, 66.3, 67.9, 71.5, 115.7, 119.8, 122.7, 127.1, 129.2, 134.7, 138.1 (broad), 159.0 (broad), 166.1 (broad), 179.3, 181.4, 184.9 and 186.4.

115. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using $\text{CuK}\alpha$ radiation: 9.2, 9.5, 10.3, 10.6, 11.9 and 12.2.

116. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $\text{CuK}\alpha$ radiation: 5.6, 8.5, 9.0, 12.4 (broad), 15.8 (broad) and 17.1–17.4 (broad).

117. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $\text{CuK}\alpha$ radiation: 4.9, 5.4, 8.0 and 12.4.

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